PATENT COOPERATION TREATY

WO 2009/034473
PCT/IB2008/003078

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
AVAILABILITY OF THE PUBLICATION
OF THE INTERNATIONAL APPLICATION

To:

BULLETT, Rachel, Margaret
Carpmaels & Ransford
43-45 Bloomsbury Square
London WC1A 2RA
ROYAUME-UNI

Date of mailing *(day/month/year)* 19 March 2009 (19.03.2009)		
Applicant's or agent's file reference P051703WO	**IMPORTANT NOTICE**	
International application No. PCT/IB2008/003078	International filing date *(day/month/year)* 12 September 2008 (12.09.2008)	Priority date *(day/month/year)* 12 September 2007 (12.09.2007)
Applicant NOVARTIS AG et al		

The applicant is hereby **notified** that the International Bureau:

☑ has **published** the above-indicated international application on 19 March 2009 (19.03.2009) under No. WO 2009/034473

☐ has **republished** the above-indicated international application on under No. WO
For an explanation as to the reason for this republication of the international application, reference is made to INID codes (15), (48) or (88) *(as the case may be)* on the front page of the published international application.

A copy of the international application is available for viewing and downloading on WIPO's website at the following address: www.wipo.int/pctdb (in the appropriate field of the structured search, enter the PCT or WO number).

The applicant may also obtain a paper copy of the published international application from the International Bureau by sending an e-mail to patentscope@wipo.int or by submitting a written request to the contact details provided below.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Authorized officer
Cecile Chatel

e-mail: ro.ib@wipo.int

The subject-matter of claim 1 therefore differs from this known D1 in that: mutations have been introduced.

The technical effect to be achieved is a GAS57 antigen with a proteolytic activity toward IL-8 that is reduced to at least 50% relative to wild-type GAS57.

The problem to be solved by the present invention may therefore be regarded as the provision of a GAS57 antigen with reduced proteolytic activity.

The solution proposed in claims 1-4 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

The production of mutants of GAS57 at positions D151, H279 and S617 are merely several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed. For example, the inactivation of Streptococcus proteases through mutation of specific residues is known from D6.

4.2 Claims 5-9, relating to fusions of mutant GAS57 antigens with carrier proteins and related subject matter, can also not be considered inventive. The use of GAS57 fusion proteins, including other GAS antigens, or bacterial carrier proteins has already been described in D1 (p.30, li.27 - p.33, li.18; p.43, li.11-19). It would therefore be obvious for the person skilled in the art, seeking to produce an immunogenic GAS57 varient, to produce fusions or carrier compositions thereof as described in D1. Moreover, it is not clear from the description what advantage mutant GAS57 immunogenic compositions possess over those of the prior art: the use of GAS57 in vaccines, and also anti-GAS57 antibodies is known (see D1 and D2). GAS57/Spy0416/ScpC has been described several times as a suitable vaccine candidate and target for therapy (D3 and D4), in particular by blocking its ability to inactivate IL-8 through proteolytic digestion (D3, p4634, col.2, para.2).

Claims 5-9 therefore lack an inventive step in accordance with Article 33(3) PCT.

5.0 Claim 19 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT.

The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information	For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.
Amending claims under Art. 19 PCT	Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.
Filing a demand for international preliminary examination	In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT). If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).
Filing informal comments	After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.
End of the international phase	At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPER (international preliminary examination report).
Relevant PCT Rules and more information	Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003

XS CPRTENFRDE

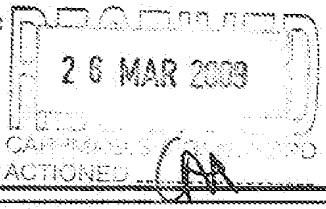
BINSDOCID: <XS_____20061101030F_1_>

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:

CARPMAELS & RANSFORD
Attn. Bullett, Rachel M.
43-45 Bloomsbury Square
London WC1A 2RA
GRANDE BRETAGNE



PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference P051703WO	Date of mailing *(day/month/year)* 27/03/2009
International application No. PCT/IB2008/003078	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant NOVARTIS AG	International filing date *(day/month/year)* 12/09/2008

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 338.82.70

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Julia Severin

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1–10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1*bis*(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43*bis*.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
P051703WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB2008/003078	12/09/2008	12/09/2007
Applicant		
NOVARTIS AG		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [X] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [X] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2008/003078

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

   a. type of material

   - [X] a sequence listing
   - [ ] table(s) related to the sequence listing

   b. format of material

   - [X] on paper
   - [X] in electronic form

   c. time of filing/furnishing

   - [X] contained in the international application as filed
   - [X] filed together with the international application in electronic form
   - [ ] furnished subsequently to this Authority for the purpose of search

2. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2008/003078

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/09 A61K39/40 C07K16/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, COMPENDEX, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/032582 A (CHIRON CORP [US]; GRANDI GUIDO [US]; TELFORD JOHN [US]; BENSI GIULIANO) 14 April 2005 (2005-04-14) P04285?EP, PP020663.0006	10-24
Y	The whole document, in particular page 33, line 19 - page 34, line 29; claims 1,10,18; sequences 116-122	1-24
X	WO 02/34771 A (CHIRON SPA [IT]; INST GENOMIC RESEARCH [US]; TELFORD JOHN [IT]; MASIGN) 2 May 2002 (2002-05-02) - P02593!EP, PP16620	10-13, 19-24
Y	The whole document, in particular page 4, line 8 - line 34; sequence 6298	1-24

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 March 2009	27/03/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Chapman, Rob

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HIDALGO-GRASS CARLOS ET AL: "A streptococcal protease that degrades CXC chemokines and impairs bacterial clearance from infected tissues" EMBO (EUROPEAN MOLECULAR BIOLOGY ORGANIZATION) JOURNAL, vol. 25, no. 19, October 2006 (2006-10), pages 4628-4637, XP002519221 ISSN: 0261-4189 The whole document, in particular page 4634, column 2, paragraph 2	1-24
Y	RODRIGUEZ-ORTEGA M J ET AL: "Characterization and identification of vaccine candidate proteins through analysis of the group A Streptococcus surface proteome" NATURE BIOTECHNOLOGY FEBRUARY 2006 NATURE PUBLISHING GROUP US, vol. 24, no. 2, February 2006 (2006-02), pages 191-197, XP002519222 The whole document, in particular the abstract	1-24
Y	NORRBY S R ET AL: "Infections due to group A streptococcus: New concepts and potential treatment strategies" ANNALS ACADEMY OF MEDICINE SINGAPORE, vol. 26, no. 5, September 1997 (1997-09), pages 691-693, XP009113742 ISSN: 0304-4602 the whole document	1-24
Y	GUBBA S ET AL: "Replacement of Histidine 340 with alanine inactivates the group A Streptococcus extracellular cysteine protease virulence factor" INFECTION AND IMMUNITY 200006 US, vol. 68, no. 6, June 2000 (2000-06), pages 3716-3719, XP002519224 ISSN: 0019-9567 the whole document	1-24
P,X	WO 2008/003515 A (INTERCELL AG [AT]; MEINKE ANDREAS [AT]; NAGY ESZTER [AT]; VON GABAIN A) 10 January 2008 (2008-01-10) The whole document, in particular sequence 56	10-24

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	ZINKERNAGEL ANNELIES S ET AL: "The IL-8 protease SpyCEP/ScpC of Group A Streptococcus promotes resistance to neutrophil killing" CELL HOST & MICROBE, vol. 4, no. 2, August 2008 (2008-08), pages 170-173, XP002519225 ISSN: 1931-3128 the whole document	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2008/003078

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005032582 A	14-04-2005	CA 2532369 A1	14-04-2005
		EP 1648500 A2	26-04-2006
		JP 2007500726 T	18-01-2007
WO 0234771 A	02-05-2002	AU 1412702 A	06-05-2002
		CA 2425303 A1	02-05-2002
		EP 1328543 A2	23-07-2003
		MX PA03003690 A	05-05-2004
		NZ 524888 A	29-09-2006
		US 2006210579 A1	21-09-2006
WO 2008003515 A	10-01-2008	AU 2007271350 A1	10-01-2008

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2008/003078	12.09.2008	12.09.2007

International Patent Classification (IPC) or both national classification and IPC
INV. A61K39/09 A61K39/40 C07K16/12

Applicant
NOVARTIS AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Chapman, Rob Telephone No. +49 89 2399-2855

Form PCT/ISA/237 (Cover Sheet) (April 2005)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☒ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☒ on paper

      ☒ in electronic form

   c. time of filing/furnishing:

      ☒ contained in the international application as filed.

      ☒ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9
	No:	Claims	10-24
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-24
Industrial applicability (IA)	Yes:	Claims	1-24
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Re Item V.

1.0 Reference is made to the following documents:

D1: WO 2005/032582 A (CHIRON CORP [US]; GRANDI GUIDO [US]; TELFORD JOHN [US]; BENSI GIULIANO) 14 April 2005 (2005-04-14)

D2: WO 02/34771 A (CHIRON SPA [IT]; INST GENOMIC RESEARCH [US]; TELFORD JOHN [IT]; MASIGN) 2 May 2002 (2002-05-02)

D3: HIDALGO-GRASS CARLOS ET AL: "A streptococcal protease that degrades CXC chemokines and impairs bacterial clearance from infected tissues" EMBO (EUROPEAN MOLECULAR BIOLOGY ORGANIZATION) JOURNAL, vol. 25, no. 19, October 2006 (2006-10), pages 4628-4637, XP002519221 ISSN: 0261-4189

D4: RODRIGUEZ-ORTEGA M J ET AL: "Characterization and identification of vaccine candidate proteins through analysis of the group A Streptococcus surface proteome" NATURE BIOTECHNOLOGY FEBRUARY 2006 NATURE PUBLISHING GROUP US, vol. 24, no. 2, February 2006 (2006-02), pages 191-197, XP002519222

D5: NORRBY S R ET AL: "Infections due to group A streptococcus: New concepts and potential treatment strategies" ANNALS ACADEMY OF MEDICINE SINGAPORE, vol. 26, no. 5, September 1997 (1997-09), pages 691-693, XP002519223 ISSN: 0304-4602

D6: GUBBA S ET AL: "Replacement of Histidine 340 with alanine inactivates the group A Streptococcus extracellular cysteine protease virulence factor" INFECTION AND IMMUNITY 200006 US, vol. 68, no. 6, June 2000 (2000-06), pages 3716-3719, XP002519224 ISSN: 0019-9567

D7: WO 2008/003515 A (INTERCELL AG [AT]; MEINKE ANDREAS [AT]; NAGY ESZTER [AT]; VON GABAIN A) 10 January 2008 (2008-01-10)

D8: ZINKERNAGEL ANNELIES S ET AL: "The IL-8 protease SpyCEP/ScpC of Group A Streptococcus promotes resistance to neutrophil killing" CELL HOST & MICROBE, vol. 4, no. 2, August 2008 (2008-08), pages 170-173, XP002519225 ISSN: 1931-3128

2.0 The present application relates to the use of mutated, protease-inactive GAS57/ScpC/Spy0416, and antibodies directed against it, for use in therapeutic compositions such as vaccines.

3.0 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 10-24 is not new in the sense of Article 33(2) PCT.

3.1 Document D1 discloses the use of GAS antigens, including GAS57 (SEQ ID NO: 116-122), for the manufacture of therapeutic compositions e.g. a vaccine, and antibodies against said GAS antigen (p.1-p.3; p.33, li.19 - p.34, li.29). Further components of the composition include adjuvants (p.38, li.7 - p.43, li.19) and carrier peptides from a bacteria or virus selected from the group consisting of N. meningitidis (including serogroup A, B, C, W135 and/or Y), Streptococcus pneumoniae, Bordetella pertussis, Moraxella catarrhalis, Tetanus, Diphtheria, Respiratory Syncytial virus ('RSV'), polio, measles, mumps, rubella, and rotavirus (p.43, li.11-19). In another embodiment, the GAS antigen combinations are combined with one or more additional, non-GAS antigens suitable for use in a vaccine designed to protect elderly or immunocomprised individuals. For example, the GAS antigen combinations may be combined with an antigen derived from the group consisting of Enterococcus faecalis, Staphylococcus aureus, Staphylococcus epidermis, Pseudomonas aeruginosa, Legionella pneumophila, Listeria monocytogenes, influenza, and Parainfluenza virus ('PIV') (p.43, li.20-25).

D1 therefore anticipates the novelty of present claims 10-24.

3.2 Document D2 discloses proteins from group B streptococcus (Streptococcus agalactiae) and group A streptococcus (Streptococcus pyogenes) for the production of antigens for vaccination, antibodies and diagnostics (p.4, li.8-li.34). One such protein corresponds to GAS57 (SEQ ID NO: 6298).

D2 therefore anticipates the novelty of present claims 10-13, and 19-24.

4.0 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-9 does not involve an inventive step in the sense of Article 33(3) PCT.

4.1 The document D1 is regarded as being the closest prior art to the subject-matter of claim 1, and discloses (the references in parentheses applying to this document): a GAS57 peptide and nucleic acid sequences (SEQ ID NO: 116-122; see also section 3.1, above).

The subject-matter of claim 1 therefore differs from this known D1 in that: mutations have been introduced.

The technical effect to be achieved is a GAS57 antigen with a proteolytic activity toward IL-8 that is reduced to at least 50% relative to wild-type GAS57.

The problem to be solved by the present invention may therefore be regarded as the provision of a GAS57 antigen with reduced proteolytic activity.

The solution proposed in claims 1-4 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

The production of mutants of GAS57 at positions D151, H279 and S617 are merely several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed. For example, the inactivation of Streptococcus proteases through mutation of specific residues is known from D6.

4.2 Claims 5-9, relating to fusions of mutant GAS57 antigens with carrier proteins and related subject matter, can also not be considered inventive. The use of GAS57 fusion proteins, including other GAS antigens, or bacterial carrier proteins has already been described in D1 (p.30, li.27 - p.33, li.18; p.43, li.11-19). It would therefore be obvious for the person skilled in the art, seeking to produce an immunogenic GAS57 varient, to produce fusions or carrier compositions thereof as described in D1. Moreover, it is not clear from the description what advantage mutant GAS57 immunogenic compositions possess over those of the prior art: the use of GAS57 in vaccines, and also anti-GAS57 antibodies is known (see D1 and D2). GAS57/Spy0416/ScpC has been described several times as a suitable vaccine candidate and target for therapy (D3 and D4), in particular by blocking its ability to inactivate IL-8 through proteolytic digestion (D3, p4634, col.2, para.2).

Claims 5-9 therefore lack an inventive step in accordance with Article 33(3) PCT.

5.0 Claim 19 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT.

The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information	For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.
Amending claims under Art. 19 PCT	Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.
Filing a demand for international preliminary examination	In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT). If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).
Filing informal comments	After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.
End of the international phase	At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPER (international preliminary examination report).
Relevant PCT Rules and more information	Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003

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